

DETAILED ACTION

Applicant's amendment filed on March 5, 2008 is acknowledged and has been entered. Claim 1 has been amended. Claim 7 has been canceled. Claims 1-6 and 8-16 are pending. Claim 17 is withdrawn from consideration as being drawn to a non-elected invention.

Claims 1-6 and 8-16 are discussed in this Office action.

All of the amendments and arguments have been thoroughly reviewed and considered but are not found persuasive for the reasons discussed below. Any rejection not reiterated in this action has been withdrawn as being obviated by the amendment of the claims. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

This action is made FINAL as necessitated by Amendment.

New Grounds of Rejection Necessitated by Amendment

Claim Rejections - 35 USC § 103

1. Claims 1-6, 8-10, 12 and 15-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Watts et al. (Journal of Pharmacology and Experimental Therapeutics, 2001, vol. 299, no. 2, p. 434-441) in view of Zammatteo et al. (Clinical Chemistry, 2002, vol. 48, no. 1, p. 25-34), Langmann et al. (Clinical Chemistry, 2003, vol. 49, no. 2, p. 230-238), Yabuuchi et al. (Biochemical and Biophysical Research Communications, 2002, vol. 299, p. 410-417), Prades et

al. (Cytogenetic Genome Research, 2002, vol. 98, p. 160-168), Neff and Neff (PNAS, 1997, vol. 94, p. 4766-4771) and List et al. (Blood, 1996, vol. 87, no. 6, p. 2464-2469). Watts teaches cDNA microarray analysis of multidrug resistance by doxorubicin selection (Abstract).

With regard to claim 1, Watts teaches a method for the determination of the resistance of cells versus the action of an active substance comprising:

- (i) providing a sample containing cells exposed or having been exposed to said active substance (p. 434, col. 1 and p. 435, col. 1, bottom paragraph, where the human multiple myeloma cell line, RPMI 8226, selected in 60 nM doxorubicin, resulting in resistant variant 8226/Dox6 and further selection in 400 nM yielding 8226/Dox40 cell lines),
- (ii) analyzing a gene expression pattern of said cells on a microarray (p. 435, col. 2, 'microarray preparation' heading, where cDNAs were printed onto chemically activated glass slides, including 5184 IMAGE consortium genes and 88 human housekeeping genes), said microarray comprising on specific locations thereon capture probes for specific detection and quantification of ATP binding cassette (ABC) transporters (Figure 2, where MDR1 and ABC transporter 1 results of microarray analysis are depicted, and also multiple additional ABC transporter genes disclosed in Table 1 of the instant application were also analyzed including ABC A2, A3, A4, ABC B1, B10, ABC C2, C13, ABC D3, ABC E1, ABC E2, as published at [//biorag.org/perl/setseq.pl?id=5h](http://biorag.org/perl/setseq.pl?id=5h); see attached sheets with representative entries for specific genes noted), wherein a change of the gene expression of said at least 5 ABC transporters by a factor of at least about 1.5 as compared to a reference is indicative of the development and/or existence of resistance of said cells to the substance (p. 436, col. 2, 'data analysis' heading, where fluorescence intensity measurements were taken and compared with background and

elements with a signal below 1.4-fold background in one channel were designated as possible cases of a gene turned on or off and genes found to be differentially expressed in four of seven hybridizations comparing control RPMI 8226 with 8226/Dox40 was considered for relevance to drug resistant phenotype).

With regard to claim 2, Watts teaches an embodiment of claim 1, wherein said analyzing of gene expression pattern is for ABC transporters selected from those listed in Table 1 (Figure 2, where MDR1 and ABC transporter 1 results of microarray analysis are depicted, and also multiple additional ABC transporter genes disclosed in Table 1 of the instant application were also analyzed including ABC A2, A3, A4, ABC B1, B10, ABC C2, C13, ABC D3, ABC E1, ABC E2).

With regard to claim 3, Watts teaches an embodiment of claim 1, wherein said at least 5 genes of the ABC transporter family are selected from the genes provided in Table 1 (Figure 2, where MDR1 and ABC transporter 1 results of microarray analysis are depicted, and also multiple additional ABC transporter genes disclosed in Table 1 of the instant application were also analyzed including ABC A2, A3, A4, ABC B1, B10, ABC C2, C13, ABC D3, ABC E1, ABC E2).

With regard to claim 5, Watts teaches an embodiment of claim 1, wherein said drug is selected from Table 3 (Abstract, p. 434, col. 1 and p. 435, col. 1, bottom paragraph, where the human multiple myeloma cell line, RPMI 8226, selected in 60 nM doxorubicin, resulting in resistant variant 8226/Dox6 and further selection in 400 nM yielding 8226/Dox40 cell lines, wherein the drug was doxorubicin).

With regard to claim 6, Watts teaches an embodiment of claim 1, wherein said cells are incubated in the presence of said drug (Abstract, p. 434, col. 1 and p. 435, col. 1, bottom paragraph, where the human multiple myeloma cell line, RPMI 8226, selected in 60 nM doxorubicin, resulting in resistant variant 8226/Dox6 and further selection in 400 nM yielding 8226/Dox40 cell lines, wherein the drug was doxorubicin).

With regard to claim 10, Watts teaches a method for monitoring a patient treated with a drug for chemotherapy, comprising the method of claims 1, 2, or 3, wherein said drug is for chemotherapy (p. 434, col. 1, where it is noted that doxorubicin is important for the treatment of a variety of cancers)

With regard to claim 15, Watts teaches an embodiment of claim 1, wherein said capture probes are single-stranded nucleotides ((p. 435, col. 2, 'microarray preparation' heading, where cDNAs were printed onto chemically activated glass slides, including 5184 IMAGE consortium genes and 88 human housekeeping genes).

With regard to claim 16, Watts teaches an embodiment of claim 1, wherein each one specific location gives the quantification of one ABC transporters gene (Figure 2, where MDR1 and ABC transporter 1 results of microarray analysis are depicted, and also multiple additional ABC transporter genes disclosed in Table 1 of the instant application were also analyzed including ABC A2, A3, A4, ABC B1, B10, ABC C2, C13, ABC D3, ABC E1, ABC E2, as published at <http://biorag.org/perl/setseq.pl?id=5h>).

Regarding claim 1, Watts does not teach that the microarray further comprises capture probes common for said subfamilies. Nef teaches a common probe for detection of variants within the same subfamily of odorant receptors (Figure 2 legend).

Regarding claim 1, Nef teaches a microarray that comprises capture probes common for subfamilies (Figure 2 legend, where COR7 subfamily hybridized with specific probes and with a common probe, COR7ab). While Nef does not teach that these common probes are common for subfamilies within ABC transporter subfamilies, based on the teaching of hybridization to common elements within a subfamily, it would have been prima facie obvious to one of ordinary skill to have applied this type of analysis to identify probes which are common to multiple members of the ABC transporter subfamilies.

Regarding claims 1 and 2, Watts does not teach the quantification of 49 human ATP binding cassette (ABC) transporters. Langmann teaches the detection and profiling of the complete ABC-transporter superfamily in a variety of tissues through real-time reverse transcription expression analysis (Abstract).

With regard to claim 1 and 2, Langmann in view of Watts, teaches the detection of 47 ABC transporter genes.

Langmann does not teach the detection of the final 2 members that round out the total family of genes at 49 as claimed. Yabuuchi teaches the cloning and characterization of ABCC13, a new member of the ABC transporter family. Prades teaches the cloning and characterization of ABCA13, a new member of the gene family (Abstract).

Therefore, when Langmann, Yabuuchi and Prades are combined, 49 ABC transporter genes are detected and quantified, meeting the limitation of claim 1 and 2.

Furthermore, regarding claim 1, neither Watts, Langmann, Yabuuchi and Prades also do not teach that said microarray is a low density microarray containing capture probes for the

detection of up to 1000 genes. Zammatteo teaches the use of a low-density microarray for the detection and monitoring of expression of MAGE-A genes.

With regard to claim 1, Zammatteo teaches a low density microarray consisting of capture probes for the detection of up to 1000 genes (p. 28, col. 1-2, where the process of constructing the MAGE DNA microarrays is described).

Finally, regarding claim 1, Watts does not teach that the cells are derived from a patient and wherein said method is designed for the determination of a potential active drug for the patient treatment.

With regard to claim 1, List teaches an embodiment of claim 6, wherein the cells are derived from a patient and wherein said method is designed for the determination of a potential active drug for the patient treatment (Table 4, where the change in drug resistance phenotype after cyclosporine treatment is examined; p. 2466, col. 1, where the response to cyclosporine treatment was described in detail).

With regard to claim 4, List teaches an embodiment of claim 1, wherein said resistance of cells is resistance of cells from a patient to the chemotherapy by a given drug (Table 4, where the change in drug resistance phenotype after cyclosporine treatment is examined; see also Table 3).

With regard to claim 8, List teaches an embodiment of any one of claims 1, 2, or 3, further comprising determining an activity of said drug against said cells (Table 4, where the change in drug resistance phenotype after cyclosporine treatment is examined; p. 2466, col. 1, where the response to cyclosporine treatment was described in detail).

With regard to claim 9, List teaches an embodiment of any one of claims 1, 2, or 3, further comprising selecting of an active drug for patient treatment (Table 4, where the change in

drug resistance phenotype after cyclosporine treatment is examined; p. 2466, col. 1, where the response to cyclosporine treatment was described in detail).

With regard to claim 10, List teaches a method for monitoring a patient treated with a drug for chemotherapy, comprising the method of any one of claims 1, 2, or 3, wherein said drug is for chemotherapy (p. 2465, col. 1, where the specific treatments of different types of chemotherapy regimens are described)

With regard to claim 12, List teaches an embodiment of claim 1, wherein said sample containing cells is from acute myeloid leukemia (Figure 1, Table 1, where AML patient samples were studied).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have extended the number of ABC transporter genes as taught by Langmann to include the two additional family members as taught by Yabuuchi and Prades to arrive at the claimed invention with a reasonable expectation for success in order to quantify 49 family members together. As taught by Langmann, “we have developed a rapid, accurate, and highly sensitive real-time reverse transcription-PCR (RT-PCR) method for detection and quantification of all 47 currently known members of the ABC transporter superfamily” (Abstract). The two additional family members, ABCC13 and ABCA13 had not been isolated prior to the publication of Langmann. Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to have extended the number of ABC transporter genes as taught by Langmann to include the two additional family members as taught by Yabuuchi and Prades to arrive at the claimed invention with a reasonable expectation for success.

Furthermore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have incorporated the low density microarray format taught by Zammateo into the method of detection of ABC transporters in multidrug resistance analysis to arrive at the claimed invention with a reasonable expectation for success. While Zammateo discloses the use of these 'low density microarrays' for the detection of MAGE-A sequences specifically, for their role in tumor immunotherapy, the process of constructing and the process of analyzing the low-density microarray would be equally applicable and useful for the detection of ABC Transporter sequences or any other sequence of interest. As taught by Zammateo, "the assay presented here can be considered an easy screening test to identify the MAGE-A genes expressed in a tumor sample" and this test is "very fast and avoids the use of hazardous compounds such as ethidium bromide". Furthermore, "because a single capture probe is used for each MAGE-A gene, the cost of the assay is reduced and the interpretation of the data is straightforward, unlike high density microarrays, which rely on a pattern of hybridization to identify one target" (p. 31, col. 2). Therefore, considering the stated benefits of the specific low-density microarray format disclosed by Zammateo one of ordinary skill in the art at the time the invention was made would have been motivated to incorporate the low density microarray format taught by Zammateo to the detection of ABC transporter genes to achieve a straightforward and fast analysis of expression of these specific target sequences with a reasonable expectation for success.

Furthermore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have incorporated the teachings of List, specifically directed to the association of multidrug resistance genes and patient response into the method of gene

expression analysis of multi-drug resistance associated genes as taught by Watts in view of Zammatteo, Langmann, Yabuuchi and Prades with a reasonable expectation of success. As taught by List, "Clinical resistance to chemotherapy results from the interaction of numerous biological variables. In this study, we found that overexpression of the novel major vault transporter protein, LRP, has prognostic significance in AML" (p. 2466, col. 2). Furthermore List teaches, "despite treatment and cohort heterogeneity, LRP was an important predictor of response to induction chemotherapy in patients with AML, independent of disease category. After adjusting for potential differences related to diagnostic group, LRP+ patients had a significantly lower remission rate and higher probability of resistant failure than did LRP- patients" (p. 2467, col. 1). While List examines the expression of the multidrug resistance genes using antibodies and immunohistochemistry and Watts in view of Zammatteo, Langmann, Yabuuchi and Prades teaches an analysis of expression at the level of mRNA using microarrays, it would have been obvious to one of ordinary skill in the art to apply the general experimental design taught by List, including an analysis of expression correlated with patient response, to include gene specific analysis in addition to analysis at the protein level. Therefore, one of ordinary skill in the art at the time that the invention was made would have been motivated to include the teachings by List, including the determination of resistance of specific patients to particular chemotherapeutic targets into the method of gene expression analysis taught by Watts with a reasonable expectation for success.

Finally, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have applied the teachings of common probes for hybridization to different members of a subfamily of odorant receptors as disclosed by Nef to the hybridization

and detection of ABC transporter subfamilies to arrive at the claimed invention with a reasonable expectation for success. As taught by Nef, “we have further characterized the chicken olfactory receptor subfamily 7 (COR7) composed of two highly related genes (named COR7a and COR7b) which are 98.5% identical” (Abstract). Nef also teaches that genomic DNA from chicken “hybridized with the specific COR7a or COR7b probes or with a common probe (COR7ab)” (Figure 2 legend). While Nef does not teach that these common probes are common for subfamilies within ABC transporter subfamilies, based on the teaching of hybridization to common elements within a subfamily, it would have been prima facie obvious to one of ordinary skill to have applied this type of analysis to identify probes which are common to multiple members of the ABC transporter subfamilies with a reasonable expectation for success.

2. Claims 4, 10 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Watts et al. (Journal of Pharmacology and Experimental Therapeutics, 2001, vol. 299, no. 2, p. 434-441) in view of Zammateo et al. (Clinical Chemistry, 2002, vol. 48, no. 1, p. 25-34), Langmann et al. (Clinical Chemistry, 2003, vol. 49, no. 2, p. 230-238), Yabuuchi et al. (Biochemical and Biophysical Research Communications, 2002, vol. 299, p. 410-417), Prades et al. (Cytogenetic Genome Research, 2002, vol. 98, p. 160-168), Neff and Neff (PNAS, 1997, vol. 94, p. 4766-4771) and List et al. (Blood, 1996, vol. 87, no. 6, p. 2464-2469) as applied to claims 1-6, 8-10, 12 and 15-16 above, and further in view of Nakayama et al. (Int J. Cancer, 2002, vol. 101, p. 488-495). Watts teaches cDNA microarray analysis of multidrug resistance by doxorubicin selection (Abstract).

Watts in view of Zammateo, Langmann, Yabuuchi, Prades, Neff and List teaches the limitations of claims 1-6, 8-10, 12 and 15-16 as recited in the 103 rejection stated above. Watts

does not explicitly teach the examination of the resistance of cells to a particular chemotherapy treatment in patient samples or the suitability of the treatment for the specific patient sample. Nakayama teaches an examination of the expression of multi-drug resistance genes in ovarian carcinoma (Abstract).

With regard to claim 4, Nakayama teaches an embodiment of claim 1, wherein said resistance of cells is resistance of cells from a patient to the chemotherapy by a given drug (Figure 1, where the expression of multidrug resistance genes were examined in 82 patients with ovarian carcinoma; p. 489, 'patients and samples' heading, where these patients were primarily treated with surgery and postoperative chemotherapy, including cisplatin 60-70 mg/m², doxorubicin 40 mg/m² and cyclophosphamide 500 mg/body).

With regard to claim 10, Nakayama teaches a method for monitoring a patient treated with a drug for chemotherapy, comprising the method of any one of claims 1, 2, or 3, wherein said drug is for chemotherapy (Figure 1, where the expression of multidrug resistance genes were examined in 82 patients with ovarian carcinoma; p. 489, 'patients and samples' heading, where these patients were primarily treated with surgery and postoperative chemotherapy, including cisplatin 60-70 mg/m², doxorubicin 40 mg/m² and cyclophosphamide 500 mg/body)

With regard to claim 14, Nakayama teaches an embodiment of claim 1, wherein said sample containing cells is from solid tumors (p. 489, col. 2, 'patient samples' heading, where surgical specimens from 82 patients with ovarian carcinoma were provided and where ovarian carcinoma is a solid tumor).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to incorporate specific patient samples, including ovarian carcinoma, as

taught by Nakayama into the gene expression analysis disclosed by Watts in view of Zammateo, Langmann, Yabuuchi and Prades with a reasonable expectation for success. Both Watts and Nakayama are centrally focused on the examination of the gene expression of genes associated with multi-drug resistance and have an interest in identifying gene targets that are specifically associated with resistance to specific chemotherapeutic drugs. Nakayama teaches “several genes including MDR1, MRP1, MRP2 and LRP genes have been identified to be responsible for resistance to various drugs” (p. 488, col. 1). Furthermore, Nakayama teaches that “during the past decade there have been a lot of studies linking various transporters to multidrug resistance both in cell culture and in clinic. Among such transporters MDR1, MRP1, MRP2, LRP and BCRP have gained considerable attention in cancer chemotherapy. We claim yet another transporter, ATP7B is involved in cisplatin drug resistance. We observed a high frequency of expressions of drug resistance-related transporters such as MDR1, MRP1, MRP2, LRP, BCRP and ATP7B gene in untreated human ovarian carcinoma.” (p. 494, col. 1, ‘discussion’ heading). Therefore, considering the common experimental focus shared between Nakayama and Watts, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the teachings of Nakayama to incorporate the microarray analysis taught by Watts or to have incorporated the patient samples and examination of drug resistance taught by Nakayama into the analysis disclosed by Watts with a reasonable expectation for success.

3. Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Watts et al. (Journal of Pharmacology and Experimental Therapeutics, 2001, vol. 299, no. 2, p. 434-441) in view of Zammateo et al. (Clinical Chemistry, 2002, vol. 48, no. 1, p. 25-34), Langmann et al.

(Clinical Chemistry, 2003, vol. 49, no. 2, p. 230-238), Yabuuchi et al. (Biochemical and Biophysical Research Communications, 2002, vol. 299, p. 410-417), Prades et al. (Cytogenetic Genome Research, 2002, vol. 98, p. 160-168), Neff and Neff (PNAS, 1997, vol. 94, p. 4766-4771) and List et al. (Blood, 1996, vol. 87, no. 6, p. 2464-2469) as applied to claims 1-6, 8-10, 12 and 15-16 above, and further in view of Dao et al. (Human Molecular Genetics, 1998, vol. 7, no. 4, p. 597-608). Watts teaches cDNA microarray analysis of multidrug resistance by doxorubicin selection (Abstract).

Watts in view of Zammateo, Langmann, Yabuuchi, Prades, Neff and List teaches the limitations of claims 1-3, 5-6, 10 and 15-16 as recited in the 102 rejection stated above. Watts does not explicitly teach the examination of Kir6.1, Mr6.2 or IMPT1. Dao teaches the isolation and characterization of an imprinted gene located on chromosome 11p15.5, IMPT1 (Abstract).

With regard to claim 11, Dao teaches an embodiment of claim 1, wherein the assay contains at least one gene selected from Kir6.1, Mr6.2 and IMPT (p. 599, Figure 2, where the tissue specific expression of IMPT1 is examined).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have extended the gene specific sequences analyzed by Watts in view of Zammateo, Langmann, Yabuuchi and Prades to incorporate the specific gene, IMPT1, as taught by Dao. As taught by Dao, "IMPT1 (imprinted multi-membrane-spanning polyspecific transporter-like gene 1), located in this chromosomal domain between IPL and p57KIP2. This gene encodes a predicted protein with multiple membrane spanning segments which belongs to the polyspecific transporter/multi-drug resistance gene family" (p. 597, col. 2). Furthermore, Dao teaches that "The predicted IMPT1 protein identified many similar proteins in a Blastp

analysis: all were members of a well-established family of membrane proteins with multiple membrane-spanning segments and with known or suspected polyspecific transport capabilities for small organic molecules” (p. 598, col. 2). Therefore, considering the stated goal of Watts of examining the expression of genes associated with multi-drug transport, one of ordinary skill in the art at the time the invention was made would have been motivated to include the additional target, IMPT1, into the gene expression analysis of resistance to chemotherapy drugs as taught by Watts with a reasonable expectation for success.

4. Claims 12-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Watts et al. (Journal of Pharmacology and Experimental Therapeutics, 2001, vol. 299, no. 2, p. 434-441) in view of Zammateo et al. (Clinical Chemistry, 2002, vol. 48, no. 1, p. 25-34), Langmann et al. (Clinical Chemistry, 2003, vol. 49, no. 2, p. 230-238), Yabuuchi et al. (Biochemical and Biophysical Research Communications, 2002, vol. 299, p. 410-417), and Prades et al. (Cytogenetic Genome Research, 2002, vol. 98, p. 160-168), Neff and Neff (PNAS, 1997, vol. 94, p. 4766-4771) and List et al. (Blood, 1996, vol. 87, no. 6, p. 2464-2469) as applied to claims 1-6, 8-10, 12 and 15-16 above, and further in view of van den Heuvel-Eibrink et al. (International Journal of Pharmacology and Therapeutics). Watts teaches cDNA microarray analysis of multidrug resistance by doxorubicin selection (Abstract).

Watts in view of Zammateo, Langmann, Yabuuchi, Prades, Neff and List teaches the limitations of claims 1-3, 5-6, 10 and 15-16 as recited in the 102 rejection stated above. Watts does not explicitly teach the examination of cells from acute myeloid leukemia or acute

lymphocytic leukemia. Van den Heuvel-Eibrink teaches an overview of the role of membrane transport-associated multidrug resistance proteins in leukemia (Abstract).

With regard to claim 12, van den Heuvel-Eibrink teaches an embodiment of claim 1, wherein said sample containing cells is from acute myeloid leukemia (p. 100-103, where the relevance of multidrug resistance and ALL and AML leukemias is discussed, specifically at p. 103, col. 2, it is noted that the coexpression of several drug resistance proteins seems to be highly predictive of clinical outcome. In AML, the expression of MRP and MDR-1 is correlated with complete remission and long-term survival).

With regard to claim 13, van den Heuvel-Eibrink teaches the method of claim 1, wherein said sample containing cells is from acute lymphocytic leukemia (p. 100-103, where the relevance of multidrug resistance and ALL and AML leukemias is discussed; specifically, at p. 100, col. 1, it is noted that the long-term survival for adults with ALL is 20%. Treatment failure is associated with clinical resistance to chemotherapy).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the teachings of Watts to incorporate specific patient samples and particularly patient samples derived from patients affected by a variety of leukemias, including acute myeloid leukemia and/or acute lymphocytic leukemia. As taught by van den Heuvel-Eibrink, "In adults, AML is the most frequently occurring leukemia and the incidence of ALL is much lower. After a CR rate of 80%, the long-term survival for adults with ALL is only 20%. Treatment failure is associated with clinical resistance to chemotherapy and with cellular resistance in vitro determined by cell culture assays" (p. 100, col. 1). Furthermore, van den Heuvel-Eibrink teaches that "Expression of *mdr-1* at transcriptional and a post-

translational level, in de novo AML has been proven as an independent adverse prognostic factor with respect to CR and survival, especially in adults and this has led to clinical studies in adults with *mdr-1* modifiers such as cyclosporin and PSC833” (p. 102, col. 2). Finally, van den Heuvel-Eibrink teaches that “*Mdr-1* expression might play a more important role in adults. Only in childhood ALL has a high expression of LRP been found at time of relapse and this was in the cases of multiple relapse. *Mdr-1* and LRP expression at diagnosis in AML patients is regarded as an independent prognostic factor for CR and long-term survival” (p. 103, col. 2, ‘discussion’ heading). Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to incorporate the additional tumor targets described by van den Heuvel-Eibrink or to apply the gene expression analysis by microarray taught by Watts to the specific tumor targets with a reasonable expectation for success.

5. Claims 1-6, 8-10, 12 and 15-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wang et al. (Chinese Journal of Cancer Research, 2002, 14(1), p. 5-10) in view of Annereau et al. (Proceedings of the American Association for Cancer Research, July 2003, vol. 44, 2nd ed, abstract #3992, p. 796-797), Zammateo et al. (Clinical Chemistry, 2002, vol. 48, no. 1, p. 25-34), Langmann et al. (Clinical Chemistry, 2003, vol. 49, no. 2, p. 230-238), Yabuuchi et al. (Biochemical and Biophysical Research Communications, 2002, vol. 299, p. 410-417), Prades et al. (Cytogenetic Genome Research, 2002, vol. 98, p. 160-168), Neff and Neff (PNAS, 1997, vol. 94, p. 4766-4771) and List et al. (Blood, 1996, vol. 87, no. 6, p. 2464-2469). Wang teaches the use of cDNA microarrays to monitor gene expression profiles in drug resistant KB cells (Abstract).

With regard to claim 1, Wang teaches a method for the determination of the resistance of cells versus the action of an active substance comprising:

(i) providing a sample containing cells exposed or having been exposed to said active substance (p. 6, 'cell culture and RNA preparation' heading, where two KB cell lines, KB3-1 and KB-V1 were cultured and RNA was extracted; KB-V1 was treated with 200 ng/ml vinblastin, an anti-cancer drug),

(ii) analyzing a gene expression pattern of said cells on a microarray (p. 6, col. 1, 'fabrication of microarrays' and 'labeling, hybridization and scanning of microarrays' heading, where cDNA microarrays, consisting of a total of 12,720 PCR products, representing 2,640 randomly picked clones from a leukocyte cDNA library and 10,080 known genes), wherein a change of the gene expression by a factor of at least about 1.5 as compared to a reference is indicative of the development and/or existence of resistance of said cells to the substance (p. 6, col. 2, 'results and discussion heading', where when labeled samples from KB-V1 cells and KB3-1 cells were co-hybridized to the array, on average approximately 0.68% of the cDNAs exhibit more than a 2-fold expression level change).

With regard to claim 5, Wang teaches an embodiment of claim 1, wherein said drug is selected from Table 3 (p. 6, 'cell culture and RNA preparation' heading, where two KB cell lines, KB3-1 and KB-V1 were cultured and RNA was extracted; KB-V1 was treated with 200 ng/ml vinblastin, an anti-cancer drug).

With regard to claim 6, Wang teaches an embodiment of claim 1, wherein said cells are incubated in the presence of said drug (p. 6, 'cell culture and RNA preparation' heading, where

two KB cell lines, KB3-1 and KB-V1 were cultured and RNA was extracted; KB-V1 was treated with 200 ng/ml vinblastin, an anti-cancer drug).

With regard to claim 10, Wang teaches a method for monitoring a patient treated with a drug for chemotherapy, comprising the method of any one of claims 1, 2, or 3, wherein said drug is for chemotherapy (p. 6, 'cell culture and RNA preparation' heading, where two KB cell lines, KB3-1 and KB-V1 were cultured and RNA was extracted; KB-V1 was treated with 200 ng/ml vinblastin, an anti-cancer drug)

With regard to claim 15, Wang teaches an embodiment of claim 1, wherein said capture probes are single-stranded nucleotides (p. 6, col. 1, 'fabrication of microarrays' and 'labeling, hybridization and scanning of microarrays' heading, where cDNA microarrays, consisting of a total of 12,720 PCR products, representing 2,640 randomly picked clones from a leukocyte cDNA library and 10,080 known genes).

Regarding claim 1, Wang does not explicitly state that said microarray comprising on specific locations thereon capture probes for specific detection and quantification of at least 5 ATP binding cassette (ABC) transporters.

With regard to claim 1, Annereau teaches a microarray comprising on specific locations thereon capture probes for specific detection and quantification of at least 5 ATP binding cassette (ABC) transporters (p. 796, Abstract #3992, lines 1-9, where they included 90 probes, specific to 36 ABC transporters).

With regard to claim 2, Annereau in view of Wang teaches an embodiment of claim 1, wherein said analyzing of gene expression pattern is for ABC transporters selected from those listed in Table 1 (p. 796, Abstract #3992, lines 1-9, where they included 90 probes, specific to 36

ABC transporters, where this collection of probes would overlap with at least 5-10 of the ABC transporters listed).

With regard to claim 3, Annereau in view of Wang teaches an embodiment of claim 1, wherein said at least 5 genes of the ABC transporter family are selected from the genes provided in Table 1 (p. 796, Abstract #3992, lines 1-9, where they included 90 probes, specific to 36 ABC transporters, where this collection of probes would overlap with at least 5-10 of the ABC transporters listed).

With regard to claim 16, Annereau teaches an embodiment of claim 1, wherein each one specific location gives the quantification of one ABC transporters gene (p. 796, Abstract #3992, lines 1-9, where they included 90 probes, specific to 36 ABC transporters).

Regarding claims 1 and 2, neither Wang or Annereau teach the quantification of 49 human ATP binding cassette (ABC) transporters. Langmann teaches the detection and profiling of the complete ABC-transporter superfamily in a variety of tissues through real-time reverse transcription expression analysis (Abstract).

With regard to claim 1 and 2, Langmann teaches the detection of 47 ABC transporter genes.

Langmann does not teach the detection of the final 2 members that round out the total family of genes at 49 as claimed. Yabuuchi teaches the cloning and characterization of ABCC13, a new member of the ABC transporter family. Prades teaches the cloning and characterization of ABCA13, a new member of the gene family (Abstract).

Therefore, when Langmann, Yabuuchi and Prades are combined, 49 ABC transporter genes are detected and quantified, meeting the limitation of claim 1 and 2.

Furthermore, regarding claim 1, neither Wang, Annereau, Langmann, Yabuuchi and Prades teach that said microarray is a low density microarray containing capture probes for the detection of up to 1000 genes. Zammatteo teaches the use of a low-density microarray for the detection and monitoring of expression of MAGE-A genes.

With regard to claim 1, Zammatteo in view of Wang and Annereau, teaches a low density microarray containing capture probes for the detection of up to 3000 genes (p. 28, col. 1-2, where the process of constructing the MAGE DNA microarrays is described).

Regarding claim 1, Wang does not teach that the microarray further comprises capture probes common for said subfamilies. Nef teaches a common probe for detection of variants within the same subfamily of odorant receptors (Figure 2 legend).

With regard to claim 1, Nef teaches a microarray that comprises capture probes common for subfamilies (Figure 2 legend, where COR7 subfamily hybridized with specific probes and with a common probe, COR7ab). While Nef does not teach that these common probes are common for subfamilies within ABC transporter subfamilies, based on the teaching of hybridization to common elements within a subfamily, it would have been prima facie obvious to one of ordinary skill to have applied this type of analysis to identify probes which are common to multiple members of the ABC transporter subfamilies.

Finally, regarding claim 1, Wang does not teach that the cells are derived from a patient and wherein said method is designed for the determination of a potential active drug for the patient treatment.

Further with regard to claim 1, List teaches an embodiment wherein the cells are derived from a patient and wherein said method is designed for the determination of a potential active

drug for the patient treatment (Table 4, where the change in drug resistance phenotype after cyclosporine treatment is examined; p. 2466, col. 1, where the response to cyclosporine treatment was described in detail).

With regard to claim 4, List teaches an embodiment of claim 1, wherein said resistance of cells is resistance of cells from a patient to the chemotherapy by a given drug (Table 4, where the change in drug resistance phenotype after cyclosporine treatment is examined; see also Table 3).

With regard to claim 8, List teaches an embodiment of any one of claims 1, 2, or 3, further comprising determining an activity of said drug against said cells (Table 4, where the change in drug resistance phenotype after cyclosporine treatment is examined; p. 2466, col. 1, where the response to cyclosporine treatment was described in detail).

With regard to claim 9, List teaches an embodiment of any one of claims 1, 2, or 3, further comprising selecting of an active drug for patient treatment (Table 4, where the change in drug resistance phenotype after cyclosporine treatment is examined; p. 2466, col. 1, where the response to cyclosporine treatment was described in detail).

With regard to claim 10, List teaches a method for monitoring a patient treated with a drug for chemotherapy, comprising the method of any one of claims 1, 2, or 3, wherein said drug is for chemotherapy (p. 2465, col. 1, where the specific treatments of different types of chemotherapy regimens are described).

With regard to claim 12, List teaches an embodiment of claim 1, wherein said sample containing cells is from acute myeloid leukemia (Figure 1, Table 1, where AML patient samples were studied).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have extended the number of ABC transporter genes as taught by Langmann to include the two additional family members as taught by Yabuuchi and Prades to arrive at the claimed invention with a reasonable expectation for success in order to quantify 49 family members together. As taught by Langmann, “we have developed a rapid, accurate, and highly sensitive real-time reverse transcription-PCR (RT-PCR) method for detection and quantification of all 47 currently known members of the ABC transporter superfamily” (Abstract). The two additional family members, ABCC13 and ABCA13 had not been isolated prior to the publication of Langmann. Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to have extended the number of ABC transporter genes as taught by Langmann to include the two additional family members as taught by Yabuuchi and Prades to arrive at the claimed invention with a reasonable expectation for success.

Furthermore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have incorporated the array disclosed by Annereau into the analysis of gene expression changes in resistant cells treated with an anti-cancer drug as disclosed by Wang to arrive at the claimed invention with a reasonable expectation for success. As taught by Annereau, “our aim was to create a high-density microarray to explore different modes of resistance against anticancer drugs. To a collection of genes known to play a role in detoxification, we added probes to detect the expression of the members of the ABC-transporter superfamily” (p. 796, abstract #3992, lines 1-4). Wang was also interested in the analysis of gene expression in multi-drug resistant cells using a cDNA microarray. As noted by Wang,

“Several mechanisms of drug resistance in tumors have been proposed, including over-expression of the multidrug resistance gene (MDR1) and the multidrug resistance-associated proteins (MRP), and increased DNA damage repair” (p. 5). While Wang does not specifically note the inclusion or exclusion of these specific targets, MDR1 and/or MRP, both members of the ABC-transporter superfamily, the specific mention of their suspected role in drug resistance suggests that if these targets were not included, one of ordinary skill in the art would have been motivated to incorporate the 36 target sequences disclosed by Annereau with a reasonable expectation for success, in order to achieve an even more precise picture of the multiple genes involved in tumor progression and drug resistance.

Furthermore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have incorporated the low density microarray format taught by Zammatteo into the method of detection of ABC transporters in multidrug resistance analysis taught by Wang in view of Annereau to arrive at the claimed invention with a reasonable expectation for success. While Zammatteo discloses the use of these ‘low density microarrays’ for the detection of MAGE-A sequences specifically, for their role in tumor immunotherapy, the process of constructing and the process of analyzing the low-density microarray would be equally applicable and useful for the detection of ABC Transporter sequences or any other sequence of interest. As taught by Zammatteo, “the assay presented here can be considered an easy screening test to identify the MAGE-A genes expressed in a tumor sample” and this test is “very fast and avoids the use of hazardous compounds such as ethidium bromide”. Furthermore, “because a single capture probe is used for each MAGE-A gene, the cost of the assay is reduced and the interpretation of the data is straightforward, unlike high density microarrays, which rely

on a pattern of hybridization to identify one target” (p. 31, col. 2). Therefore, considering the stated benefits of the specific low-density microarray format disclosed by Zammateo one of ordinary skill in the art at the time the invention was made would have been motivated to incorporate the low density microarray format taught by Zammateo to the detection of ABC transporter genes to achieve a straightforward and fast analysis of expression of these specific target sequences with a reasonable expectation for success.

Furthermore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have incorporated the teachings of List, specifically directed to the association of multidrug resistance genes and patient response into the method of gene expression analysis of multi-drug resistance associated genes as taught by Wang in view of Annereau, Zammateo, Langmann, Yabuuchi and Prades with a reasonable expectation of success. As taught by List, “Clinical resistance to chemotherapy results from the interaction of numerous biological variables. In this study, we found that overexpression of the novel major vault transporter protein, LRP, has prognostic significance in AML” (p. 2466, col. 2). Furthermore List teaches, “despite treatment and cohort heterogeneity, LRP was an important predictor of response to induction chemotherapy in patients with AML, independent of disease category. After adjusting for potential differences related to diagnostic group, LRP+ patients had a significantly lower remission rate and higher probability of resistant failure than did LRP- patients” (p. 2467, col. 1). While List examines the expression of the multidrug resistance genes using antibodies and immunohistochemistry and Wang in view of Annereau, Zammateo, Langmann, Yabuuchi and Prades teaches an analysis of expression at the level of mRNA using microarrays, it would have been obvious to one of ordinary skill in the art to apply the general

experimental design taught by List, including an analysis of expression correlated with patient response, to include gene specific analysis in addition to analysis at the protein level. Therefore, one of ordinary skill in the art at the time that the invention was made would have been motivated to include the teachings by List, including the determination of resistance of specific patients to particular chemotherapeutic targets into the method of gene expression analysis taught by Wang with a reasonable expectation for success.

Finally, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have applied the teachings of common probes for hybridization to different members of a subfamily of odorant receptors as disclosed by Nef to the hybridization and detection of ABC transporter subfamilies to arrive at the claimed invention with a reasonable expectation for success. As taught by Nef, “we have further characterized the chicken olfactory receptor subfamily 7 (COR7) composed of two highly related genes (named COR7a and COR7b) which are 98.5% identical” (Abstract). Nef also teaches that genomic DNA from chicken “hybridized with the specific COR7a or COR7b probes or with a common probe (COR7ab)” (Figure 2 legend). While Nef does not teach that these common probes are common for subfamilies within ABC transporter subfamilies, based on the teaching of hybridization to common elements within a subfamily, it would have been *prima facie* obvious to one of ordinary skill to have applied this type of analysis to identify probes which are common to multiple members of the ABC transporter subfamilies with a reasonable expectation for success.

6. Claims 1-4, 6, 8-10, 12 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al. (Journal of Pharmaceutical Sciences, 2003, vol. 92, no. 11, p. 2152-2163) in view

of Langmann et al. (Clinical Chemistry, 2003, vol. 49, no. 2, p. 230-238), Zammateo et al. (Clinical Chemistry, 2002, vol. 48, no. 1, p. 25-34), Yabuuchi et al. (Biochemical and Biophysical Research Communications, 2002, vol. 299, p. 410-417), Prades et al. (Cytogenetic Genome Research, 2002, vol. 98, p. 160-168), Neff and Neff (PNAS, 1997, vol. 94, p. 4766-4771) and List et al. (Blood, 1996, vol. 87, no. 6, p. 2464-2469). Lee teaches an examination of the expression of multi-drug resistance proteins by RT-PCR and microarray analysis (Abstract).

With regard to claim 1, Lee teaches a method for the determination of the resistance of cells versus the action of an active substance comprising:

- (i) providing a sample containing cells exposed or having been exposed to said active substance (p. 2153-2154, 'MRP functional assay' heading, where cells were preincubated with or without 5-CDFA in the presence or absence of indomethacin; 'Rh123 efflux assay' heading, where cells were preincubated with Rh123; 'tissue culture' heading, where cells were also incubated with IL-6, IL-1 β , TNF- α),
- (ii) analyzing a gene expression pattern of said cells on a microarray (p. 2154, col. 2, 'microarray studies' heading), said microarray comprising on specific locations thereon capture probes for specific detection and quantification of ATP binding cassette (ABC) transporters wherein said microarray is a low density microarray containing capture probes for the detection of up to 3000 genes (Figure 1, where MDR1/ABCB1 expression was analyzed in HuH7 cells, Figure 2, where MDR1/ABCB1 expression was analyzed in HepG2 cells, Figure 4C, where the expression of MRP1, MRP2, MRP3, MRP6 were measured in HepG2 cells; p. 2157, col. 2, where the microarray expression results were measured), wherein a change of the gene expression of said at least 5 ABC transporters by a factor of at least about 1.5 as compared to a reference is

indicative of the development and/or existence of resistance of said cells to the substance (p. 2157, col. 2, where the microarray expression results were measured).

With regard to claim 2, Lee teaches an embodiment of claim 1, wherein said analyzing of gene expression pattern is for ABC transporters selected from those listed in Table 1 (Figure 1, where MDR1/ABCB1 expression was analyzed in HuH7 cells, Figure 2, where MDR1/ABCB1 expression was analyzed in HepG2 cells, Figure 4C, where the expression of MRP1, MRP2, MRP3, MRP6 were measured in HepG2 cells; p. 2157, col. 2, where the microarray expression results were measured).

With regard to claim 3, Lee teaches an embodiment of claim 1, wherein said analyzing of gene expression pattern for at least 5 genes of the ABC transporter family having unravelled multi-drug resistance function as provided in Table 1 (Figure 1, where MDR1/ABCB1 expression was analyzed in HuH7 cells, Figure 2, where MDR1/ABCB1 expression was analyzed in HepG2 cells, Figure 4C, where the expression of MRP1, MRP2, MRP3, MRP6 were measured in HepG2 cells; p. 2157, col. 2, where the microarray expression results were measured).

With regard to claim 6, Lee teaches an embodiment of claim 1, wherein said cells are incubated in the presence of said drug (p. 2153-2154, 'MRP functional assay' heading, where cells were preincubated with or without 5-CDFA in the presence or absence of indomethacin; 'Rh123 efflux assay' heading, where cells were preincubated with Rh123; 'tissue culture' heading, where cells were also incubated with IL-6, IL-1 β , TNF- α).

With regard to claim 15, Lee teaches an embodiment of claim 1, wherein said capture probes are single-stranded nucleotides (p. 2154-2155, 'microarray studies', where fluorescently labeled cDNA was hybridized onto Human 1.7K cDNA microarrays).

Regarding claim 1, while Lee teaches the examination of 5 ABC transporters, Lee does not teach that at least 5 ABC transporter subfamilies were detected. Langmann teaches the detection and profiling of the complete ABC-transporter superfamily in a variety of tissues through real-time reverse transcription expression analysis (Abstract).

With regard to claim 1, Langmann teaches an embodiment of claim 1, wherein said microarray contains capture probes to at least 5 ABC transporter subfamilies and wherein a change in detection of at least 5 ABC transporters was detected (Table 1, where gene specific primers and probes for all of the members of the ABC transporter superfamily are noted and see Table 2, where the change in gene expression for the ABC transporters was detected).

Regarding claim 1, Langmann in view of Lee, teaches the detection of 47 ABC transporter genes.

Langmann does not teach the detection of the final 2 members that round out the total family of genes at 49 as claimed. Yabuuchi teaches the cloning and characterization of ABCC13, a new member of the ABC transporter family. Prades teaches the cloning and characterization of ABCA13, a new member of the gene family (Abstract).

Therefore, when Langmann, Yabuuchi and Prades are combined, 49 ABC transporter genes are detected and quantified, meeting the limitation of claim 1 and 2.

Furthermore, regarding claim 1, neither Lee, Langmann, Yabuuchi or Prades teach that said microarray is a low density microarray containing capture probes for the detection of up to 1000 genes.

With regard to claim 1, Zammatteo in view of Wang and Annereau, teaches a low density microarray containing capture probes for the detection of up to 3000 genes (p. 28, col. 1-2, where the process of constructing the MAGE DNA microarrays is described).

Regarding claim 1, Lee does not teach that the microarray further comprises capture probes common for said subfamilies. Nef teaches a common probe for detection of variants within the same subfamily of odorant receptors (Figure 2 legend).

With regard to claim 1, Nef teaches a microarray that comprises capture probes common for subfamilies (Figure 2 legend, where COR7 subfamily hybridized with specific probes and with a common probe, COR7ab). While Nef does not teach that these common probes are common for subfamilies within ABC transporter subfamilies, based on the teaching of hybridization to common elements within a subfamily, it would have been prima facie obvious to one of ordinary skill to have applied this type of analysis to identify probes which are common to multiple members of the ABC transporter subfamilies.

Finally, regarding claim 1, Lee does not teach that the cells are derived from a patient and wherein said method is designed for the determination of a potential active drug for the patient treatment.

Further with regard to claim 1, List teaches an embodiment wherein the cells are derived from a patient and wherein said method is designed for the determination of a potential active drug for the patient treatment (Table 4, where the change in drug resistance phenotype after

cyclosporine treatment is examined; p. 2466, col. 1, where the response to cyclosporine treatment was described in detail).

With regard to claim 4, List teaches an embodiment of claim 1, wherein said resistance of cells is resistance of cells from a patient to the chemotherapy by a given drug (Table 4, where the change in drug resistance phenotype after cyclosporine treatment is examined; see also Table 3).

With regard to claim 8, List teaches an embodiment of any one of claims 1, 2, or 3, further comprising determining an activity of said drug against said cells (Table 4, where the change in drug resistance phenotype after cyclosporine treatment is examined; p. 2466, col. 1, where the response to cyclosporine treatment was described in detail).

With regard to claim 9, List teaches an embodiment of any one of claims 1, 2, or 3, further comprising selecting of an active drug for patient treatment (Table 4, where the change in drug resistance phenotype after cyclosporine treatment is examined; p. 2466, col. 1, where the response to cyclosporine treatment was described in detail).

With regard to claim 10, List teaches a method for monitoring a patient treated with a drug for chemotherapy, comprising the method of any one of claims 1, 2, or 3, wherein said drug is for chemotherapy (p. 2465, col. 1, where the specific treatments of different types of chemotherapy regimens are described).

With regard to claim 12, List teaches an embodiment of claim 1, wherein said sample containing cells is from acute myeloid leukemia (Figure 1, Table 1, where AML patient samples were studied).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have extended the method of expression analysis taught by Lee to

incorporate the variety of additional ABC transporter family targets as taught by Langmann to arrive at the claimed invention with a reasonable expectation for success. As taught by Langmann, “several ABC proteins in the human system are responsible for drug exclusion in compound-treated tumor cells providing cellular mechanisms for the development of multi-drug resistance”. Langmann also states that there is a “need for a sensitive, rapid, and accurate method for quantification of ABC transporter expression and a systematic investigation of these molecules in human tissues is thus warranted” (p. 230-231). Langmann also notes “the aim of this study was to establish step by step, a complete panel of TaqMan RT-PCR assays for all 47 currently known human ABC molecules” (p. 231). Finally, Langmann notes “we provide comprehensive data on the expression of all human ABC transporter genes in various tissues” and while Langmann notes “TaqMan real-time RT-PCR is much more sensitive than blot-based mRNA analysis tools” because much less starting material is necessary prior to analysis, Langmann also notes “the results obtained from our assay are consistent with those obtained in Northern blot and in situ hybridization studies with single ABC molecules” (p. 237, col. 1, bottom of column). In comparison to Langmann, Lee teaches the analysis of MRP1, 2, 3 and 6 and MDR1 mRNA using RT-PCR and microarray analysis. Lee notes “the use of microarrays provides the speed, ease and feasibility of monitoring the differential expression profile of hundreds of genes.” Lee also notes “it has been reported that cDNA microarray detection of large changes in gene expression is often comparable with data obtained from Northern blots” and states, too “a major strength of cDNA microarray technology is in its ability to rapidly detect large 10- to 100-fold increases in gene expression” (p. 2161, col. 1). Therefore, considering the combined teachings of Langmann and Lee, it would have been *prima facie* obvious to one of

ordinary skill in the art to extend the targets taught by Lee to incorporate additional ABC transporter sequences and tissue specific expression as taught by Langmann to achieve more comprehensive data regarding the role of additional ABC transporter family members in multi-drug resistance with a reasonable expectation for success.

Furthermore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have extended the number of ABC transporter genes as taught by Langmann to include the two additional family members as taught by Yabuuchi and Prades to arrive at the claimed invention with a reasonable expectation for success in order to quantify 49 family members together. As taught by Langmann, “we have developed a rapid, accurate, and highly sensitive real-time reverse transcription-PCR (RT-PCR) method for detection and quantification of all 47 currently known members of the ABC transporter superfamily” (Abstract). The two additional family members, ABCC13 and ABCA13 had not been isolated prior to the publication of Langmann. Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to have extended the number of ABC transporter genes as taught by Langmann to include the two additional family members as taught by Yabuuchi and Prades to arrive at the claimed invention with a reasonable expectation for success.

Furthermore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have incorporated the low density microarray format taught by Zammatteo into the method of detection of ABC transporters in multidrug resistance analysis taught by Lee in view of Langmann to arrive at the claimed invention with a reasonable expectation for success. While Zammatteo discloses the use of these ‘low density microarrays’

for the detection of MAGE-A sequences specifically, for their role in tumor immunotherapy, the process of constructing and the process of analyzing the low-density microarray would be equally applicable and useful for the detection of ABC Transporter sequences or any other sequence of interest. As taught by Zammattco, “the assay presented here can be considered an easy screening test to identify the MAGE-A genes expressed in a tumor sample” and this test is “very fast and avoids the use of hazardous compounds such as ethidium bromide”. Furthermore, “because a single capture probe is used for each MAGE-A gene, the cost of the assay is reduced and the interpretation of the data is straightforward, unlike high density microarrays, which rely on a pattern of hybridization to identify one target” (p. 31, col. 2). Therefore, considering the stated benefits of the specific low-density microarray format disclosed by Zammattco one of ordinary skill in the art at the time the invention was made would have been motivated to incorporate the low density microarray format taught by Zammattco to the detection of ABC transporter genes to achieve a straightforward and fast analysis of expression of these specific target sequences with a reasonable expectation for success.

Furthermore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have incorporated the teachings of List, specifically directed to the association of multidrug resistance genes and patient response into the method of gene expression analysis of multi-drug resistance associated genes as taught by Lee in view of Langmann, Yabuuchi and Prades with a reasonable expectation of success. As taught by List, “Clinical resistance to chemotherapy results from the interaction of numerous biological variables. In this study, we found that overexpression of the novel major vault transporter protein, LRP, has prognostic significance in AML” (p. 2466, col. 2). Furthermore List teaches,

“despite treatment and cohort heterogeneity, LRP was an important predictor of response to induction chemotherapy in patients with AML, independent of disease category. After adjusting for potential differences related to diagnostic group, LRP+ patients had a significantly lower remission rate and higher probability of resistant failure than did LRP- patients” (p. 2467, col. 1). While List examines the expression of the multidrug resistance genes using antibodies and immunohistochemistry and Lee in view of Langmann, Yabuuchi and Prades teaches an analysis of expression at the level of mRNA using microarrays, it would have been obvious to one of ordinary skill in the art to apply the general experimental design taught by List, including an analysis of expression correlated with patient response, to include gene specific analysis in addition to analysis at the protein level. Therefore, one of ordinary skill in the art at the time that the invention was made would have been motivated to include the teachings by List, including the determination of resistance of specific patients to particular chemotherapeutic targets into the method of gene expression analysis taught by Lee with a reasonable expectation for success.

Finally, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have applied the teachings of common probes for hybridization to different members of a subfamily of odorant receptors as disclosed by Nef to the hybridization and detection of ABC transporter subfamilies to arrive at the claimed invention with a reasonable expectation for success. As taught by Nef, “we have further characterized the chicken olfactory receptor subfamily 7 (COR7) composed of two highly related genes (named COR7a and COR7b) which are 98.5% identical” (Abstract). Nef also teaches that genomic DNA from chicken “hybridized with the specific COR7a or COR7b probes or with a common probe (COR7ab)” (Figure 2 legend). While Nef does not teach that these common probes are common

for subfamilies within ABC transporter subfamilies, based on the teaching of hybridization to common elements within a subfamily, it would have been prima facie obvious to one of ordinary skill to have applied this type of analysis to identify probes which are common to multiple members of the ABC transporter subfamilies with a reasonable expectation for success.

Response to Arguments

7. Applicant's arguments filed March 5, 2008 have been fully considered but they are not persuasive. Applicant's arguments with respect to claims 1-6 and 8-16 have been considered but are moot in view of the new ground(s) of rejection. However, insofar as the arguments apply to the new grounds of rejection, these arguments will be addressed.

Applicant has amended claim 1 to recite the limitations of claim 7 and to include an additional limitation where the microarray further comprises capture probes common for said subfamilies. A new ground of rejection in view of List, as applied previously over claim 7, and in view of ??, as providing a teaching of detection of members of a subfamily using common microarray probes.

Further, Applicant argues that Langmann teaches an advantage which "resides in a reduction of the amount of starting material to 25-50 ng" and argue that this represents a teaching away from a combination with Watts because the advantage would be abandoned.

This argument is not persuasive. While Applicant is correct that the method disclosed by Langmann allows for a reduction in starting material for expression profiling, this does not represent a teaching away from the combination with Watts. First, it is noted that Langmann is

not relied upon for the amount of starting material necessary for practice of the method. On the contrary, Langmann is relied upon specifically for the analysis of 47 of the 49 ABC transporter genes. As noted by Langmann, "we have developed a rapid, accurate and highly sensitive real-time reverse transcription PCR (RT-PCR) method for detection and quantification of all 47 currently known members of the ABC transporter superfamily", which represents a clear motivation to combine with the microarray of Watts, which would achieve an additional platform for the rapid and accurate detection of the members of the transporter superfamily. Therefore, the rejection is maintained, in view of the newly cited references.

The remaining arguments are moot as they point out features of the claims as amended that have been addressed with new grounds of rejection.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to STEPHANIE K. MUMMERT whose telephone number is (571)272-8503. The examiner can normally be reached on M-F, 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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